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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/185, 47/48, C12Q 1/37 — A3

(11) International Publication Number: **WO 99/43311**

(43) International Publication Date: 2 September 1999 (02.09.99)

(21) International Application Number: PCT/US99/04336

(22) International Filing Date: 26 February 1999 (26.02.99)

(30) Priority Data:
60/075,994 26 February 1998 (26.02.98) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
14 October 1999 (14.10.99)

(54) Title: CONJUGATED SURAMIN OR DERIVATIVES THEREOF WITH PEG, POLYASPARTATE OR POLYGLUTAMATE FOR CANCER TREATMENT

(57) Abstract

The present invention provides an assay that identifies compounds which inhibit cleavage of HGF/SF by serum proteases such as uPA, and methods in which such compounds are provided to reaction solutions, to cultured cells *in vitro*, or to a mammal *in vivo*, to inhibit cleavage of HGF/SF and to inhibit chemical and biological effects resulting from the activation of c–Met receptor by HGF/SF. The invention also provides methods for modifying suramin and suramin–related polysulfonated compounds that inhibit HGF/SF cleavage, by attaching PEG or polyanions such as polyglutamate or polyaspartate to the compounds to reduce cellular uptake of the compounds, thereby reducing their cytotoxicity. Also provided are a pharmaceutical composition containing at least one polysulfonated HGF/SF cleavage–inhibiting compound other than suramin, and a pharmaceutical composition containing at least one HGF/SF cleavage–inhibiting form of suramin or a suramin–related polysulfonated compound that is modified by conjugation to a chemical moiety that reduces uptake of the compound into cells. The present invention further includes methods wherein such pharmaceutical compositions are administered to a mammal with a tumor that is stimulated to grow by HGF/SF, to inhibit the growth or metastasis of the tumor in the mammal.

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INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/US 99/04336

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/185 A61K47/48 C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1999	01/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pilling, S

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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information on patent family members

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#5165 THE ANGIOGENESIS INHIBITOR THROMBOSPONDIN-1 PLUS IRINOTECAN SIGNIFICANTLY INHIBIT TUMOR GROWTH IN HUMAN COLON TUMOR BEARING NUDE MICE. Giaeomo Allegrini, F. A Goulette, J. W Darnowski, and P. Calabresi, *Brown Univ, Providence, RI, and Rhode Island Hosp, Providence, RI*

Our aim was to evaluate the antineoplastic activity of thrombospondin-1 (TSP), a 450Kda antiangiogenic glycoprotein plus irinotecan (CPT-11) in nude mice bearing xenografts of the human colon tumor cell line HT29. As expected, preliminary studies revealed that these agents did not interact in vitro to produce enhanced tumor cell cytotoxicity. For in vivo studies, nude mice were inoculated s.c. in the left axillary region with 5×10^6 HT29 cells. When tumors were palpable (~50mg) mice were divided into groups (n=15–22) to receive no treatment, TSP alone (5–40mg/kg, ip), CPT-11 alone (100–300mg/kg, ip), or TSP (20mg/kg) + CPT-11 (150mg/kg). TSP was injected daily while CPT-11 was administered on days 0,7,14, and 21. Mice were weighed and tumors measured twice weekly. By day 28, TSP alone (10 or 20mg/kg) significantly ($p<0.05$) inhibited tumor growth and T/C (treated tumor size/control tumor size) equaled 0.64 or 0.57, respectively. Treatment with the other doses of TSP was less effective. CTP-11 alone, at all doses, also significantly ($p<0.001$) inhibited tumor growth with an average T/C of 0.3. However, CPT-11 at 250 and 300 mg/kg induced significant toxicity and mortality. When TSP was combined with CTP-11 a highly significant inhibition of tumor growth was observed vs control (T/C=0.1 with $p=0.00002$) and vs CPT-11 alone ($p=0.0008$), without significant toxicity. These findings reveal that combinations of chemotherapy and inhibitors of angiogenesis hold significant clinical promise and warrant further evaluation. (supported by RIH and the TJ Martell Found.)